REMARKS

Reconsideration of the present application is requested in view of the foregoing amendments and the following remarks.

I. Amendments to the Claims

Prior to entry of the foregoing amendment, claims 1, 2, 25-28, 31, 35, and 36 were pending.

Claims 1, 2, 25-28, 31, and 35 are requested to be cancelled without disclaimer or prejudice to further prosecution on the merits.

Claim 36 currently is amended to correct a grammatical error and to recite "a subject" rather than "the subject."

Claims 37-42 are requested to be added. Claims 37-42 depend from claim 36 and recite the subject matter of previous claims 1, 2, 25-28, and 31, respectively.

These amendments do not introduce new matter and otherwise are proper. For these reasons, entry thereof is requested. After entry of the amendments, claims 37-42 are pending.

II. New Matter Rejection of Claim 35

Claim 35 was rejected for allegedly introducing new matter. Claim 35 has been cancelled obviating the rejection.

III. Claim Rejection - Scope of Enablement

Claims 1, 2, 25-28, 31, 35, and 36 were rejected under 35 U.S.C. § 112, first paragraph, allegedly for lack of enablement. Specifically, the Office Action states:

> 8. Newly amended Claims 1-2, 25-28, 31, 35, 36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting methylation in DAPK, FAS, MCTS, p16, PAX5, THBS, TRANCE, VHL in human genes, does not reasonably provide enablement for characterizing any breast cancer based upon methylation profiles for DAPK, FAS, MCTS, p16, PAX5, THBS, TRANCE, VHL in any subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

As stated in the Office Action, the specification is enabling for "a method" of detecting methylation in DAPK, FAS, MCTS, p16, PAX5, THBS, TRANCE, and VHL in human genes. Accordingly, claim 36 recites "a method" for detecting methylation in DAPK, FAS, MCTS, p16, PAX5, THBS, TRANCE, and VHL in human genes. New claims 37-42 depend from claim 36 and recite "a method" for detecting methylation in DAPK, FAS, MCTS, p16, PAX5, THBS, TRANCE, and VHL in human genes. Claim 1, as originally presented and as previously presented, recited "a method" for detecting methylation in human genes and was not rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement in an Office Action dated July 19, 2006; in an Office Action dated January 16, 2007, or in an Office Action dated November 30, 2007. Therefore, for these reasons, Applicants request that the Examiner reconsider and withdraw the rejection for lack of enablement with respect to the pending claims.

The claimed method also has a specific, substantial, and credible use. With respect to a utility for the claimed methods, Applicants refer to the Levenson Declaration which shows that the claimed method can be utilized for determining a subject's likelihood of having breast cancer, in particular, ductal breast cancer in situ (DCIS).

The claimed methods include steps in which the methylation of promoters of eight genes is determined. These include DAPK (otherwise known in the art as "death associated protein kinase"), FAS (otherwise known in the art as "apoptosis stimulating fragment"), MCT1 (otherwise known in

the art as the "multiple copies of T-cell malignancy" gene and which is synonymous with "MCTS1"), p16 (which encodes a ~16 kDa protein and is otherwise known in the art as "CDKN2A"), PAX5 (otherwise known in the art as "paired box protein 5"), THBS (otherwise known in the art as "thrombospondin"), TRANCE (otherwise known in the art as "tumor necrosis factor ligand superfamily member 11" or "TNFSF11"), and VHL (otherwise known in the art as "Von Hippel-Lindau disease tumor suppressor").

The Levenson Declaration describes a Grant Proposal and in particular Table 3 in which ten (10) genes are utilized as a biomarker for ductal carcinoma in situ (DCIS), which is a Stage 0 cancer and is the earliest form of breast cancer.

Table 3. Genes of the biomarker and their methylation in plasma of DCIS patients and healthy controls.

Gene	DCIS	Normal
DAPK1	89.3%	51.9%
FAS	82.8%	33.3%
MCTS1	66.7%	28.6%
CDKN2A	74.1%	35.3%
PAX5	75.0%	40.0%
PGK1	78.6%	37.5%
RPL15	53.8%	13.0%
THBS	82.1%	36.8%
TNFSF11	72.7%	30.0%
VHL	91.3%	25.0%

The ten (10) genes in Table 3 were utilized to diagnose DCIS in plasma from twenty-nine (29) patients with a sensitivity of 84% and a specificity of 80%.

Table 4. DCIS detection in plasma.

	DCIS	Normal
pDCIS	84.48%	19.87%
pNormal	15.52%	80.13%

As such, the present claims recite eight (8) of the ten (10) genes listed in Table 3, including DAPK, FAS, MCTS, p16, PAX5, THBS, TRANCE, and VHL. The Applicants respectfully submit that the methylation status of these eight (8) genes in plasma can be utilized to assess the likelihood that a subject has breast cancer, in particular ductal breast cancer in situ. Table 3 shows that:

DAPK exhibits methylation in 89.3% of DCIS patient samples versus 51.9% of normal patient samples;

FAS exhibits methylation in 82.8% of DCIS patient samples versus 33.3% of normal patient samples;

MCTS exhibits methylation in 66.7% of DCIS patient samples versus 28.6% of normal patient samples;

P16 (*i.e.*, CDKN2A) exhibits methylation in 74.1% of DCIS patient samples versus 35.3% of normal patient samples;

PAX5 exhibits methylation in 75.0% of DCIS patient samples versus 40.0% of normal patient samples;

THBS exhibits methylation in 82.1% of DCIS patient samples versus 36.8% of normal patient samples;

TRANCE (*i.e.*, TNFSF11) exhibits methylation in 72.7% of DCIS patient samples versus 30.0% of normal patient samples; and

VHL exhibits methylation in 91.3% of DCIS patient samples versus 25.0% of normal patient samples.

Therefore, any one of these listed genes exhibits differential methylation in DCIS patient samples versus normal patient samples. The claims require assessing the methylation status of each of the eight (8) recited genes. For these reasons, the claimed method has a specific, substantial, and credible use with respect to indicating that a patient has an increased likelihood of DCIS.

Furthermore, the Applicants respectfully submit that the methylation status of the promoter of p16 (*i.e.*, CDKN2A) in plasma is recognized in the art as having utility for assessing a subject's likelihood of having breast cancer (*See, e.g.*, Sharma et al., "Promoter hypermethylation of p16INK4a, p14ARF, CyclinD2 and Slit2 in serum and tumor DNA from breast cancer patients," Life Sci. 2007 Apr 24;80(20):1873-81 (full copy provided herewith); and Tan *et al.*, "Detection of promoter hypermethylation in serum samples of cancer patients by methylation-specific polymerase chain reaction for tumour suppressor genes including *RUNX3*," Oncology Reports 18: 1225-1230, 2007 (full copy provided herewith)). In particular, Tan *et al.* show that the promoter of p16 in DNA from serum samples was hypermethylated in 7/19 breast cancer patients and was not hypermethylated in 10 healthy serum controls. (*See* Abstract and page 1228, Table 1.) Therefore, the methylation status of p16 in plasma alone is recognized as having utility for assessing a subject's likelihood of having breast cancer.

For these reasons, reconsideration and withdrawal of the rejection for lack of enablement are requested.

IV. Claim Rejections – Indefiniteness of Claims 36

Claim 36 was rejected for indefiniteness with respect to reciting "the subject" rather than "a subject." Claim 36 has been amended to recite "a subject." Therefore, reconsideration and withdrawal of the rejection are requested.

V. Conclusion

The Applicants have attempted in earnest to respond to the outstanding Office Action. Allowance of the pending claims is requested. If the Examiner believes that a conference will facilitate prosecution of the application, the Examiner is requested to contact Applicants' representative below.

Respectfully submitted,

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